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(71) Applicant (for all designated states except US):
**HENKEL KOMMANDITGESELLSCHAFT AUF
AKTIEN** (DE/DE); Henkelstr. 67, D-40589 Dusseldorf
(DE)

(72) Inventor; and

(75) Inventor/Applicant (US only): SATTLER, Andrea
(DE/DE);

Himmelgeisterstr. 187, 40225 Dusseldorf (DE).
FORSTER, Thomas (DE/DE); Adalbert-Stifter-Str. 15,
D-40699 Erkrath (DE), **SCHLOTMANN, Kordula**
(DE/DE); Christophstr. 46, 40255 Dusseldorf (DE).
WEISS, Albrecht (DE/DE); Forellenweg 37, 40764
Langenfeld (DE).

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(54) Title: CLEANING AGENTS WHICH CONTAIN SURFACTANTS AND ENZYME INHIBITORS

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(57) Abstract: The invention relates to cleaning agents which contain inhibitors for the proteases that are involved in breaking down desmosomes. Said inhibitors significantly decrease drying out of the skin caused by surfactants and, as a result, improve the appearance of the skin. Suitable inhibitors are, for example, boric acid and derivatives thereof, 4-(2-aminoethyl)phenylsulfonyl fluoride (Pefablac® and Pefablac® SC), the pentapeptide sequence glycine-poline-phenylalanine-proline-leucine, and derivatives which contain this pentapeptide sequence, and are rosemary acid as well as the active ingredient Elhibin® that is obtained from leguminous seeds.

“Cleaning Agents Which Contain Surfactants and Enzyme Inhibitors”

The invention relates to compositions containing surfactants that contain enzyme inhibitors as bioactive components.

Cleaning agents, for example body-cleansing products and in particular household cleaning agents, often lead on frequent use to more or less significant drying and defatting of the skin with increased flaking. In order to make skin-protective cleansing possible, for one thing, skin-friendly surfactants are used and also so-called emollients are added to many cleaning agents.

There is a particular profile of requirements for cleansing agents that can be used even for dry skin and skin with a tendency to become dry. The occurrence of dry skin has been extensively studied (K. Kitamura, K. Yamada, A. Ito and M. Fukuda, J. Soc. Cosm. Chem. Japan 29(2), 133-145 (1995)), but the underlying biochemical processes have so far not been fully clarified.

Healthy skin is constantly renewed by a flow equilibrium which maintains the thickness of the middle layer of the skin. The cells of the horny layer (stratum corneum) on the surface of the skin are flaked off, while new cells are supplied from the basal stratum. In the flaking process (desquamation), the protein structures (desmosomes), which are responsible for the cohesion of the cells, are detached (A. Lundstrom, T. Egelrud, J. invest. Dermatol., 91, 340-343 (1988) and 94, 216-220 (1990); idem., Arch dermatol. Res. 282, 234-237 (1990)). The degradation of the desmosomes results by way of the proteases contained in the stratum corneum, of which two will be characterized in more detail. These are serine proteases of the chymotrypsin and trypsin type (T. Egelrud et al., Acta Derm. Venereol., 71, 471-474 (1991); JP 8068781 A2).

Dry skin is characterized by an intensified flaking off of keratinocytes in the epidermis.

The cleaning products used at present still cannot influence the drying out of the skin satisfactorily. The problem was to develop cleaning products that reduce the flaking of the keratinocytes by means of targeted bioactive components, so that they inhibit the proteases involved in the degradation of the desmosomes.

Surprisingly, a group of inhibitors has now been found that inhibit the proteases taking part in the flaking reaction of the skin and retain the keratinocytes in the cellular bond longer. As bioactive components in cleaning agents, they reduce the flaking process that is abnormally intensified especially in dry skin, and thus normalize the appearance of the skin that is exposed to the surfactant-containing agents. In the same way, skin protection is achieved with irritated and therefore severely flaking skin.

The subject of the invention is therefore a cleaning agent containing surfactants, characterized by the fact that it contains at least one inhibitor for the proteases involved in desmosome degradation that, at a concentration of at least 0.0005% by weight, produces at least 5% inhibition. The subject of the invention is also the use of the agent in accordance with the invention for the topical prophylactic and/or cosmetic treatment of dry skin as well as a method for cleaning and simultaneous inhibition or lessening of the drying out of the skin, characterized by the fact that the skin and integumentary appendages are treated with an agent containing surfactant and at least one inhibitor that inhibits the proteases involved in the desmosome degradation. The subject of the invention is also a method for manual cleaning of hard surfaces with surfactant-containing cleaning agents with simultaneous prevention or lessening of the drying out of the skin, characterized by the fact that the surfaces are treated with a surfactant-containing

cleaning agent that contains at least one inhibitor that inhibits the proteases involved in desmosome degradation.

Water-soluble inhibitors with a molecular weight of less than 5000 g/mol can be preferred for the purposes of the invention; by water-solubility is understood a minimal solubility of the inhibitor of 0.001% by weight in water at 25°C. Inhibition or restraint for the purposes of the invention is understood to be the decrease in activity (Definition of Enzyme Activity, cf. key word "Enzyme" in: CD Rompp Chemistry Lexicon, Version 1.0, Stuttgart, New York: Georg Thieme Verlag 1995) of the corresponding enzyme isolated from the skin or a suitable model system in the presence of the inhibitor or a mixture of inhibitors in the *in vitro* test and/or the diminished flaking off of keratinocytes on skin biopsies in the presence of the inhibitor or a mixture of inhibitors. The inhibitor or mixture of inhibitors is preferably contained in a concentration of 0.0001 to 20% by weight, particularly 0.1 to 5% by weight in the compositions. For the purposes of the invention, an agent is considered to contain surfactants that contains at least 5% by weight of a surfactant or mixture of surfactants. Among the agents in accordance with the invention are, among others, bath salts, shower preparations, shampoos, rinsing agents, soaps and household cleaners. Depending on the purpose, the surfactant-containing solutions can contain, besides the usual anionic, cationic, non-ionic and amphoteric surfactants, stabilizing components, conditioners and skin-conditioning active substances, among others.

Preferred as inhibitors in accordance with the invention are boric acid and/or its derivatives, 4-(2-aminoethyl)phenyl-sulfonyl fluoride, compounds containing the pentapeptide sequence glycine-proline-phenylalanine-proline-leucine, rosmarinic acid and Elhibin®, since they have been shown to be particularly effective.

For the purposes of the invention, inhibitors are preferred that inhibit the serine-proteinases participating in desmosome degradation. These proteinases contain in the active center an L-serine residue, essential for the catalysis. Suitable as inhibitors for the purposes of the invention are substances that modify the L-serine residue and/or block the substrate-cleavage site by interaction with the L-serine residue or with amino acids from the environment, and/or by way of the changing of the tertiary structure of the enzyme effectuate its inactivation. An inhibitory effect for the purposes of the invention, as already explained for the general case, is a decrease in activity of the serine-proteinases in the presence of the inhibitor in the *in vitro* test and/or the decreased flaking off of keratinocytes on skin biopsies in the presence of the inhibitor.

Particularly preferred for the purposes of the invention is an inhibitor that inhibits the proteinases involved in the degradation of the desmosomes such as trypsin- or chymotrypsin-like serine-proteinases. Trypsin is an endopeptidase that results in the small intestine from the precursor trypsinogen formed in the pancreas by cleavage of a hexapeptide. Characteristic for this serine-proteinase is a negatively charged L-aspartate residue in the substrate binding site which has an influence on the specificity of the enzyme. Trypsin cleaves peptide chains specifically on the carboxy side of the basic amino acids L-lysine and L-arginine. Chymotrypsin arises in the pancreas from inactive precursors, so called zymogens, by the action of trypsin. Chymotrypsin cleaves proteins, peptides, amino acid esters and amides specifically on the carboxy group of hydrophobic amino acids. Both types of enzymes participate in the degradation of the protein structures (desmosomes) that are responsible for the cohesion of the corneal cells in the skin. An inhibitory effect for the purposes of the invention, as already explained for the general case, is described as a decrease in activity of the trypsin- or chymotrypsin-like serine-proteinases in the presence of the inhibitor in the *in vitro* test and/or the decreased flaking off of keratinocytes on skin biopsies in the presence of the inhibitor.

Preferred as inhibitor is boric acid, a derivative of boric acid or a mixture of these substances (Example 1 and 2). Among the derivatives that can be used in accordance with the invention are esters and salts of boric acid and also C₁-C₅-alkyl- or aryl-substituted boric acid derivatives, such as for example phenylboric acid and/or its mono- or di-esters with C₁-C₅-alkyl residues. The use of boric acid acetate or

phenylboric acid acetate can be preferred for the purposes of the invention. Boric acid and phenylboric acid have a weakly antiseptic action. In enzyme-containing washing agents, phenylboric acid is known as an inhibitor for proteolytic enzymes, in order to raise their stability on storage. The use of phenylboric acid $C_6H_5B(OH)_2$ as an activity regulator for α -chymotrypsin in tissue cultures was taught in JP 08157800. In particular, phenylboric acid is shown in the *in vitro* test (Example 1) in very tiny concentrations (0.1%) to be an extremely effective inhibitor of chymotrypsin, an enzyme that is involved in the degradation of desmosomes. Also, in the flaking off test on skin biopsies, boric acid and phenylboric acid (Examples 8 and 9) are shown to be inhibitors and therefore particularly suitable for the surfactant-containing cleaning agents in accordance with the invention.

Just as preferentially suitable as an inhibitor is 4-(2-aminoethyl)phenylsulfonyl fluoride. Two forms of this inhibitor are known under the trade names Pefabloc® and Pefabloc% SC. The substance is described as a non-toxic, irreversible and effective inhibitor of serine proteases (C. Dentan et al., Biochemica et Biophysica Acta 1299, 353-357 (1996)). Particularly because of its low toxicity, 4-(2-aminoethyl)phenylsulfonyl fluoride is particularly suitable as an inhibitor in surfactant-containing cleaning agents. A significant inhibition of trypsin and chymotrypsin was observed in *in vitro* tests at 0.02% or 0.05% of the inhibitor, and an almost complete inhibition occurs when 0.5% is used (Example 3). This is in agreement with the result of the desquamation test on skin biopsies, in which 0.5% of the inhibitor reduces the flaking off of the corneocytes by ca. 90% (Example 10).

Likewise preferentially suitable as an inhibitor is the pentapeptide glycine-proline-phenylalanine-proline-leucine (GPFPL) or chemical derivatives that contain this pentapeptide sequence. The pentapeptide is known as an inhibitor for serine-proteinases. Also claimed for the purposes of the invention are, among others, terminal group-protected derivatives of this pentapeptide sequence, polypeptides, proteins and other chemical derivatives that contain this pentapeptide sequence and that display an inhibitory effect in the tests described on the next page. A clear inhibition of chymotrypsin (27%) was observed in *in vitro* tests when 0.33% by weight N-CBZ-Gly-Pro-Phe-Pro-Leu (N-CBZ = N-benzoyloxycarbonyl) was used (Example 4). When 0.5% N-CBZ-GPFPL is used, the desquamation of the skin can be reduced by half (Example 11).

Also particularly preferentially suitable as an inhibitor is rosmarinic acid. Rosmarinic acid is known for its inflammation-inhibiting, cytostatic and antiviral action. In cosmetics, rosemary extract is used for bath additives and as an additive in hair care products. In skin care products, rosmarinic acid is used with other active substances as a synergistically acting antioxidant combination. Among the derivatives that can be used in accordance with the invention are esters and salts of rosmarinic acid as well as C_1 - C_5 -alkyl or aryl esters. An almost complete inhibition of trypsin was observed in *in vitro* tests on use of 0.05% rosmarinic acid (example 5). When 1.0% rosmarinic acid is used, the desquamation of the skin can be reduced by about 70% (Example 12).

Also preferred as an inhibitor is Elhibin® (Pentapharm AG), obtained by a special method from leguminous seeds. Elhibin® inhibits leucocyte elastase and fibroblast elastase, which are involved in inflammatory and aging processes of the skin. The active substance is used in skin cosmetics to improve the general appearance of the skin. In the *in vitro* test, even at a concentration of 0.5%, Elhibin® inhibits both trypsin and chymotrypsin almost completely (Example 6). In the desquamation test on skin biopsies, when 1.0% Elhibin® is used the flaking off of corneocytes is reduced by more than 90% (Example 13).

Surfactants

Inhibitor active substances can be incorporated into all the usual formulations for cleaning agents. Since an abundance of such generic formulations is known to one skilled in the art, they will not be listed in detail here. Besides water and the obligatory surfactants and also physiologically suitable solvents, the formulations can also contain, among other things, skin conditioning components (e.g. oils, waxes, fats, emollient substances), thickeners and colorants and fragrances. The composition can, depending on the

requirement, be formulated almost water-free, as an aqueous or alcoholic solution, as a gel or as a surfactant-containing O/W or W/O emulsion. For suitable formulation principles, the formulations usual in cosmetics (K. Schrader, Principles and Formulations of Cosmetics, 2nd Ed., Huthig Buch Verlag, Heidelberg 1989, Pages 709-722, 606-618) may be referred to here.

Preferably, the compositions contain water-soluble surfactants that foam strongly. Among these are for example anionic surfactants or a combination of anionic surfactants with alkyl-polyglycosides.

Anionic surfactants

Preferred as anionic surfactants are solid or powdered alkyl sulfates, alkyl ether carboxylates, isethionates such as for example acylisethionates, alkyl sulfosuccinates and the monoesters of the sulfosuccinates. However, alkyl sulfonates, alkyl ether sulfates and sulfonates, alkyl succinates, diesters of sulfosuccinates, N-acylsarcosinates and N-acyltaurines with linear alkyl or acyl groups (12-18 carbon atoms) can be used in amounts that make tableting possible without agglutination. The anionic surfactants are usually used in the form of their alkali, magnesium, ammonium or alkanolammonium salts.

Sulfates

Preferred as alkyl(en)yl sulfates are the alkali, in particular sodium salts of the sulfuric acid semiester of the C₁₂-C₁₈-fatty alcohols from natural fats, for example, coconut alcohol, tallow alcohol, lauryl, myristyl, cetyl and stearyl alcohol. Also suitable are the alkali and sodium salts of the sulfuric acid semiester of the C₁₀-C₂₀-oxoalcohols and the semiesters of secondary alcohols of these chain lengths. Also preferred are alk(en)yl sulfates of the chain length mentioned, which contain a synthetic straight-chain alkyl residue produced on a petrochemical basis, that have a degradation behavior analogous to that of the appropriate compounds based on lipochemical raw materials. For intensive foam formation, at physiologically tolerated temperatures, the C₁₂-C₁₆-alkyl sulfates, and particularly the C₁₂-C₁₄-alkyl sulfates are preferred. 2-Alkyl sulfates, such as are prepared for example in US 3,234,258 or 5,075,041, are suitable anionic surfactants.

Excellent foaming properties are displayed by alkyl ether sulfates. Preferred in this group are sulfuric acid monoesters of straight-chain or branched C₇-C₂₁-alcohols ethoxylated with 1 to 6 moles ethylene oxide, such as 2-methyl-branched C₉-C₁₁-alcohols with an average of 3.5 moles ethylene oxide (EO) or C₁₂-C₁₈-fatty alcohols with 1 to 4 EO. Because of their good foaming behavior, they can be added in relatively small amounts.

Other suitable anionic surfactants of the sulfate type are sulfated fatty acid glycerol esters. Fatty acid glycerol esters are understood to be the mono-, di- and triesters and their mixtures, such as are obtained in the preparation by esterification of one mole glycerol with 1 to 3 moles fatty acid or in the transesterification of triglycerides with 0.3 to 2 moles glycerol. Preferred sulfated fatty acid glycerol esters are the esters of saturated fatty acids with 6 to 22 carbon atoms, for example caproic acid, caprylic acid, capric acid, myristic acid, lauric acid, palmitic acid, stearic acid or behenic acid.

In addition, ethoxylated alkylphenol ether sulfates, C₅-C₁₇-acyl-N-(C₁-C₄)-alkylglucamine sulfate and -N-(C₁-C₂-hydroxyalkyl)-glucamine sulfate as well as sulfates of alkylpolyglucosides can be used as anionic surfactants.

Sulfonates

Surfactants of the sulfonate type that are to be considered are preferably C₉₋₁₃-alkylbenzenesulfonates and olefinsulfonates. Olefinsulfonates are mixtures of alkene- and hydroxyalkanesulfonates and disulfonates, such as are obtained from C₁₂₋₁₈-monoolefins with terminal or interior double bonds by sulfonation with

gaseous sulfur trioxide followed by alkaline or acid hydrolysis of the sulfonation product. Also suitable are alkanesulfonates that are obtained from C₁₂-C₁₈-alkanes for example by sulfochlorination or sulfoxidation followed by hydrolysis or neutralization. Also suitable are the esters of α -sulfofatty acids (ester sulfonates), e.g. the α -sulfonated methyl ester of hydrogenated coconut, palm kernel or tallow fatty acids.

Other suitable anionic surfactants of the sulfonate type that are particularly strong foam formers are the salts, particularly the alkali metal salts, of the alk(en)ylsulfosuccinic acids, which are also called sulfosuccinates or sulfosuccinic acid esters. Among these are the mono- and/or diesters of sulfosuccinic acid with alcohols, preferably fatty alcohols and in particular ethoxylated fatty alcohols. The ethoxylated fatty alcohols can display a normal or narrow homolog distribution. Preferred sulfosuccinates contain C₈-C₁₈- fatty alcohol residues or mixtures of these. Preferably, the sulfosuccinates contain an ethoxylated fatty alcohol residue.

Non-ionic surfactants

In the non-ionic surfactant group are above all alkoxyated alcohols, alkoxyated fatty acid esters, alkylpolyglucosides and amine oxides. Moreover, fatty acid alkanolamides and fatty acid alkanolamide ethoxylates can be used as foam stabilizers.

Alkoxyated fatty alcohols

Alkoxyated fatty alcohols, depending on the degree of alkoxylation and the length of the alkyl residue, have different application technological properties. They are, among other things, used as emulsifiers and solubilizers for fats and oils in shower and foaming bath products. Advantageously used are ethoxylated alcohols, in particular primary alcohols preferably with 8 to 18 carbon atoms and an average of 1 to 12 moles ethylene oxide (EO) per mole of alcohol. The alkyl residue can be linear or preferably methyl-branched in the 2-position. Mixtures of alkoxyated alcohols with linear and methyl-branched residues, such as commonly arise with oxoalcohols, can also be used. Preferred are alcohol ethoxylates with 2-8 EO and linear C₁₂-C₁₈-alkyl residues from alcohols of natural origin that are obtained for example from coconut, palm, or tallow oils or olive or sunflower oils. Particularly preferred are the C₁₂₋₁₄-alcohols with 3 EO or 4 EO, C₉₋₁₁-alcohols with 7 EO, C₁₃₋₁₅-alcohols with 3 EO, 5 EO, 7 EO or 8 EO, C₁₂₋₁₈-alcohols with 3 EO, 5 EO, or 7 EO and mixtures of these, such as mixtures of C₁₂₋₁₄-alcohols with 3 EO, and C₁₂₋₁₈-alcohols with 5 EO. The levels of ethoxylation given are statistical averages that for a specific product can be a whole or fractional number. Also alcohol ethoxylates with a narrow distribution of homologs (narrow range ethoxylates, NRE) can be used. In addition to these non-ionic surfactants, fatty alcohols with more than 12 EO can also be used. Examples of this are tallow alcohol with 14 EO, 25 EO, 30 EO or 40 EO.

Alkylpolyglucosides

Furthermore, other non-ionic surfactants that can be used are alkylglycosides that are prepared from sugars and alcohols by acetal formation. These surfactants are particularly well tolerated by the skin and in combination with anionic surfactants present particularly stable foams with fine bubbles.

For the purposes of the invention, anhydrous sugar surfactants such as are described in DE 43 40 015 and DE 44 04 633 are preferred. Also, sprayable anhydrous APG/non-ionic surfactant mixtures such as are described in DE 198 58 923.3 can be advantageous.

The sugar components of the alkylglycosides (glycoses) that are to be considered are preferably glucose, but also fructose, mannose, galactose, talose, gulose, allose, idose, arabinose, xylose, lyxose, ribose and mixtures thereof. Preferable because of the easy availability and the good use properties are the acetal formation products of glucose with fatty alcohols that can be obtained for example from natural oils and

fats by known methods. However, polysaccharides such as for example starch and maltodextrin and the oxo- and Ziegler alcohols obtainable from technical alcohol syntheses are suitable starting materials.

With regard to the glycoside residue, both monoglycosides and also oligoglycosides in which a sugar residue is bound glycosidically to the fatty alcohol are suitable. Usually, in the commercial products, mixtures of mono- and oligoglycosides are present, which in turn represent mixtures of different isomeric forms.

Preferable are alkylglycosides of formula $R'O(G)_x$, in which R' represents a primary straight chain or methyl-branched, especially an aliphatic residue methyl-branched in the 2-position, with 8 to 22, preferably 12 to 18 carbon atoms, and G is a glucose unit with 5 or 6 carbon atoms, preferably glucose. The degree of oligomerization x , which gives the distribution of monoglycosides and oligoglycosides, is any number between 1 and 10; preferably, x is 1-2, in particular 1.1-1.4.

Preferentially used are linear alkylpolyglucosides, that is, alkylglycosides based on glucose and an n-alkyl residue.

Alkoxyated fatty acids and fatty acid esters

Another class of non-ionic surfactants that can be used in accordance with the invention is alkoxyated, preferably ethoxylated or ethoxylated/propoxylated fatty acid esters, preferably of alcohols with 1 to 4 carbon atoms or glycerol, for example the alkoxyated fatty acid methyl esters that are described in the Japanese patent application JP 58217598 or that are prepared according to the method described in the international patent application WO-A-90/13533.

Amine oxides

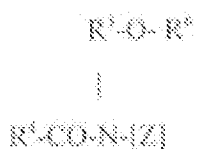
Amine oxides are obtained by the reaction of tertiary amines with hydrogen peroxide. They are easily water-soluble, biologically degradable surfactants that because of their mild cleaning action, outstanding skin tolerance, foam stability and low toxicity are particularly suitable for bath products. Among these are for example N-cocoalkyl-N,N-dimethylamine oxide and N-tallow-alkyl-N,N-dihydroxyethylamine oxide.

Polyhydroxy fatty acid amides

Polyhydroxy fatty acid amides, particularly in combination with anionic surfactants, display good foam stability. They are biologically degradable and very well tolerated by the skin.

Polyhydroxy fatty acid amides of the formula $R^2CONR^3[Z]$, in which R^2CO is an aliphatic acyl residue with 6 to 22 carbon atoms, R^3 is hydrogen, an alkyl or hydroxyalkyl residue with 1 to 4 carbon atoms and $[Z]$ is a linear or branched polyhydroxyalkyl residue with 3 to 10 carbon atoms and 3 to 10 hydroxyl groups, are suitable. The polyhydroxy fatty acid amides are known substances that can usually be obtained by reductive amination of a reducing sugar with ammonia, an alkylamine or an alkanolamine, followed by acylation with a fatty acid, a fatty acid alkyl ester or a fatty acid chloride.

Compounds of the formula



also belong to the polyhydroxy fatty acid amides group, in which R^4 is a linear or branched alkyl or alkylene residue with 7 to 12 carbon atoms, R^5 is a linear, branched or cyclic alkyl residue or an aryl residue with 2 to 8 carbon atoms and R^6 is a linear, branched or cyclic alkylene residue or an arylene residue or an oxyalkyl residue with 1 to 8 carbon atoms, with C_{1-4} -alkyl or phenyl residues being preferred. [Z] is a linear polyhydroxyalkyl residue in which the alkyl chain is substituted by at least two hydroxyl groups, or alkoxylated, preferably ethoxylated or propoxylated derivatives of this residue.

[Z] is preferably obtained by reductive amination of a reduced [sic] sugar, for example glucose, fructose, maltose, lactose, galactose, mannose or xylose. The N-alkoxy- or N-aryloxy-substituted compounds can then for example be converted to the desired polyhydroxy fatty acid amides in accordance with the International Patent Application WO-A-95/07331 by reaction with fatty acid methyl esters in the presence of an alkoxide as a catalyst.

Ampholytic surfactants

Ampholytic surfactants can also be contained in the preparations in accordance with the invention. Besides good toleration by the skin and mucosae, they have good foaming and cleaning capacity and sometimes display microbicidal activity. Ampholytic surfactants are understood to be those surface active compounds that in addition to a C_8 - C_{18} -alkyl or acyl group in the molecule contain at least one free amino group and at least one $-COOH$ or $-SO_3H$ group. They have the property of reacting like cationic surfactants in acidic solution by protonation on the tertiary nitrogen atom and of reacting like anionic surfactants in alkaline medium by salt formation on the carboxyl group. Ampholytic surfactants can form inner salts. Examples of suitable ampholytic surfactants are N-alkylglycines, N-alkylpropionic acids, N-alkylaminobutyric acids, N-alkyliminodipropionic acids, N-hydroxyethyl-N-alkylamidopropylglycines, N-alkyltaurines, N-alkylsarcosines, 2-alkylaminopropionic acids and alkylaminoacetic acids with in each case with 8 to 18 carbon atoms in the alkyl group. Particularly preferred ampholytic surfactants are N-cocoalkylaminopropionate, cocoacylaminoethylaminopropionate, C_{12-18} -acylsarcosines and cocoamphoglycinate. The commercially available product known by the trade name Dehyton® G is for example in the latter group.

Zwitterionic surfactants

Zwitterionic surfactants have likewise been known for a long time and are used in numerous cosmetic formulations. Zwitterionic surfactants are those surface active compounds that have in the molecule at least one quaternary ammonium group and at least one $-COO^{(-)}$ or $-SO_3^{(-)}$ group. The best known and most widespread group of these surfactants is that of the betaine surfactants in which the quaternary ammonium group bears two methyl substituents. Suitable zwitterionic betaine surfactants are, among others, N-alkyl-N,N-dimethylammonium glycinate, for example cocoalkyldimethylammonium glycinate, N-acyl-aminopropyl-N,N-dimethylammonium glycinate, for example cocoacylaminoethylaminopropyl-N,N-dimethylammonium glycinate, and 2-alkyl-3-carboxymethyl-3-hydroxyethyl-imidazoline, in each case with 8 to 18 carbon atoms in the alkyl or acyl group, as well as cocoacylaminoethylhydroxyethylcarboxymethyl glycinate, which are known by the INCI designation of cocamidopropylbetaine, in particular Cocoamidopropylbetaine which is derived from C_8 - C_{18} coconut or palm kernel fatty acids. Such products are for example marketed under the trade name Dehyton® K.

Skin care components (optional)

The surfactant-containing composition in accordance with the invention can also contain a number of skin care components. For the purposes of the invention, skin care components are generally understood to be compounds that exert a conditioning influence on the skin. Among these are lipophilic compounds, such as for example hydrocarbons, silicone oils, higher alcohols and fatty acids, and also fats, oils and waxes that have an emollient effect on the skin, or curatively or systemically acting substances such as for

example ceramides, which can compensate for a deficiency in corneal lipids. Vitamins, lipoproteins, glycolipids, phospholipids and plant extracts with dermatologically active substances can be used as skin care components.

Natural and synthetic oils and fats

Among these are, among others, the fatty acid and fatty alcohol esters, particularly the monoesters of fatty acids with alcohols with 1 to 24 carbon atoms or with glycerol. This group of products involves the products of the esterification of fatty acids with 8 to 24 carbon atoms such as for example caproic acid, caprylic acid, 2-ethylhexanoic acid, capric acid, lauric acid, isotridecanoic acid, myristic acid, palmitic acid, palmoleic acid, stearic acid, isostearic acid, oleic acid, elaidic acid, petroselinic acid, linoleic acid, linolenic acid, elaeostearic acid, arachidic acid, gadoleic acid, behenic acid and erucic acid and their technical mixtures which arise for example in the pressurized cleavage of natural fats and oils or the dimerization of unsaturated fatty acids, with alcohols such as for example isopropyl alcohol, caproyl alcohol, caprylic alcohol, 2-ethylhexyl alcohol, capryl alcohol, lauryl alcohol, isotridecyl alcohol, myristyl alcohol, cetyl alcohol, palmoleyl alcohol, stearyl alcohol, isostearyl alcohol, oleyl alcohol, elaidyl alcohol, petroseliny alcohol, linolyl alcohol, linolenyl alcohol, elaeostearyl alcohol, arachyl alcohol, gadoleyl alcohol, behenyl alcohol, erucyl alcohol and brassidyl alcohol and their technical mixtures which arise in the high pressure hydrogenation of technical methyl esters based on fats and oils or of aldehydes from the Roelen oxosynthesis as well as monomer fractions in the dimerization of unsaturated fatty alcohols. The hydrogenated or hardened alcohols, e.g. hydrogenated soybean oil, castor oil and peanut oil can be used.

Oily substances that are also suitable are vaselines, paraffin oils and silicone oils. Among the latter are, among others, dialkyl- and alkylarylsilanes such as for example dimethylpolysiloxanes and methylphenylpolysiloxanes, as well as their alkoxyated and quaternized analogs.

Fatty alcohols with 8 to 22 carbon atoms

The fatty alcohols used can be saturated or unsaturated and linear or branched. Useful for the purposes of the invention are for example decanol, octanol, octenol, dodecenol, decenol, octadienol, dodecadienol, decadienol, oleyl alcohol, eruca alcohol, ricinol alcohol, stearyl alcohol, isostearyl alcohol, cetyl alcohol, lauryl alcohol, myristyl alcohol, arachidyl alcohol, capryl alcohol, capric alcohol, linoleyl alcohol, linolenyl alcohol and behenyl alcohol, and their Guerbet alcohols. The fatty alcohols are usually obtained from the esters of the fatty acids by reduction. According to the invention, fatty alcohol cuts that result from the reduction of naturally available fats and oils, such as for example beef tallow, peanut oil, colza oil, cottonseed oil, soybean oil, sunflower oil, palm kernel oil, flax oil, castor oil, corn oil, rape oil, sesame oil, cocoa butter and coconut fat. However, synthetic alcohols can also be used, e.g. the linear, even-numbered fatty alcohols of the Ziegler synthesis (Alfole®) or the partially branched alcohols from oxosynthesis (Dobanole®).

Proteins and protein derivatives

Among these are water-soluble proteins or water-soluble derivatives of insoluble proteins, in particular hydrolysates of elastin, collagen, keratin, milk albumen, soybean protein, silk protein, yeast protein, pea protein, almond protein and wheat protein, their condensation products with fatty acids and also quaternized protein hydrolysates.

Vitamins and vitamin precursors

Vitamins and vitamin precursors such as tocopherols, Vitamin A, niacinic acid and niacinamide, other vitamins of the B complex, Vitamin C, Vitamin F and in particular, biotin. Preferred in this group of skin-conditioning active substances are panthenol, its derivatives, particularly the ester and ether of

panthenol and derivatives of panthenol obtained cationically. Individual representatives are for example panthenol triacetate, panthenol monoethyl ether and its monoacetate as well as cationic panthenol derivatives.

Plant extracts or the active substances obtained from them

Plant extracts that are usually prepared by extraction of the entire plant, but in individual cases also exclusively from the flowers and/or leaves of the plant, in particular dried extracts, can be suitable as skin care components. With regard to the plant extracts that can be used in accordance with the invention, the extracts are particularly indicated that are listed in the Table beginning on page 44 of the 3rd edition of the Handbook on the Declaration of the Ingredients of Cosmetic Agents, published by the Industrial Association of Body Care Agents and Detergents e.V. (IKW), Frankfurt. In particular, extracts of oak bark, stinging nettle, hamamelis, hops, camomile, burdock root, horsetail, hawthorn, lime blossoms, almond, aloe vera, pine needles, horse chestnut, sandalwood, juniper berries, coconut, mango, apricot, lemon, wheat, kiwi, melon, orange, grapefruit, sage, rosemary, birchwood, mallow, lady's smock, wild thyme, yarrow, thyme, melissa, papilionaceous plants, coltsfoot, marsh mallow, meristem, ginseng, and ginger root can be used. Particularly preferred are the extracts from almond, aloe vera, coconut, mango, apricot, lemon, wheat, kiwi and melon. Mixtures of several different plant extracts can also be contained in the agents in accordance with the invention. The extraction agents for preparation of the plant extracts cited can be, among others, water, alcohols and their mixtures. Specific active substances or plant extract concentrates can be obtained by evaporation of the extracts.

Other skin care components

- Honey extracts that are obtained analogously to the plant extracts and usually contain 1 to 10% by weight, in particular 3-5% by weight of active substance.
- Phospholipids, for example soybean lecithin, egg lecithin and cephalins
- Bubble-forming lipids, such as for example: lecithin, cholesterol, sitosterol, ceramides, cerebrosides and sphingomyelins
- If applicable, enzymes, e.g. proteases, amylases, lipases, cellulases.

Fragrances

Fragrances are an important olfactory component of the surfactant-containing composition. They are added to the agents in accordance with the invention to improve the esthetic impression of the product, and to make available to the user, in addition to the washing and conditioning activities, a sensorily "typical and unchanging" product. Individual odoriferous compounds can be used as perfume oils or fragrances, e.g. synthetic products such as esters, ethers, aldehydes, ketones, alcohols and hydrocarbons. Odoriferous substances of the ester type can be for example benzyl acetate, phenoxyethyl isobutyrate, p-tert-butylcyclohexyl acetate, linalyl acetate, dimethylbenzylcarbinyl acetate, phenylethyl acetate, linalyl benzoate, benzyl formate, ethylmethylphenyl glycinate, allylcyclohexyl propionate, styrallyl propionate and benzyl salicylate. Among the ethers are for example benzyl ethyl ether, aldehydes are for example the linear alkanals with 8 to 18 carbon atoms, citral, citronellal, citronellyl oxyacetaldehyde, cyclamenaldehyde, hydroxycitronellal, lilyal and bourgeonal, ketones are e.g. the ionones, α -isomethylionone and methylcedryl ketone, alcohols are anethols, citronellol, eugenol, geraniol, linalool, phenylethyl alcohol and terpineol, hydrocarbons are mainly the terpenes such as limonene and pinene. Preferred, however, are mixtures of different odoriferous substances that together elicit an appealing fragrance. Such perfume oils can also contain natural mixtures of odoriferous substances such as are obtainable from plant sources, e.g. pine, citrus, jasmine, patchouli, rose or ylang-ylang oil. Also suitable are muscatel, salvia oil, camomile oil, clove oil, melissa oil, mint oil, cinnamon leaf oil, lime flower oil, juniper berry oil, vetiver oil, olibanum oil, galbanum oil, ladanum oil, as well as orangeblossom oil, neroli oil, orangepeel oil and sandalwood oil. Generally, the content of fragrances is 1-5% of the composition.

Investigation of the inhibitory effect

The inhibitory action of the protease inhibitors was demonstrated both *in vitro* on suitable model systems and also on biopsies of human skin.

1. Inhibitory effect on a serine-protease (in vitro)

Since the proteases specific to the skin that are involved in desmosome degradation were not available in sufficient quantities, the serine-proteases trypsin and chymotrypsin (Sigma) from beef pancreas serve as model enzymes to test the inhibitory action of the inhibitors used in accordance with the invention: phenylboric acid, boric acid, N-CBZ-Gly-Pro-Phe-Pro-Leu, Pefabloc® and Pefabloc® SC (Boehringer-Mannheim), rosmarinic acid and Elhibin®. As a comparison, t-AMCHA (trans-4-(aminoethyl)-cyclohexanecarboxylic acid), known as a t-PA inhibitor (*tissue-type plasminogen activator*), was also tested.

Method:

The demonstration of the chymotrypsin enzyme activity takes place using a modification analogous to the information in the *Sigma Quality Control Test Procedure* data sheet for chymotrypsin. For samples without inhibitor, 1.42 ml reagent A (80 mM Tris/HCl buffer, pH = 7.8; 25°C) was added to the test sample. For samples with inhibitor, 1.32 ml Reagent A was added to the test sample and also 0.1 ml of a solution of the appropriate inhibitor in Reagent A (concentration series). The enzyme activity was determined spectrophotometrically by conversion of the substrate N-benzoyl-L-tyrosine ethyl ester (BTEE) to N-benzoyl-L-tyrosine and ethanol. The absorption of the proteolytically split off N-benzoyl-L-tyrosine is measured at 256 nm.

The detection of the trypsin enzyme activity also takes place with a modification analogous to the information in the *Sigma Quality Control Test Procedure* data sheet for trypsin. Instead of aprotinin (Reagent F), the inhibitors in accordance with the invention were used here. For this, a series of concentrations of the inhibitors in reagent E was used. The enzyme activity was determined spectrophotometrically by conversion of the substrate N α -benzoyl-DL-arginine p-nitroaniline (BAPNA) to N α -benzoyl-DL-arginine and p-nitroaniline. The absorption of the proteolytically split off p-nitroaniline is measured at 405 nm.

The reaction kinetics were detected every 5 min at 25°C, with the linear rise in the absorption (A) per time unit (t) being a measure for the activity of the enzyme ($\Delta A/\Delta t$). The activity of the enzyme in the absence of a proteinase inhibitor ($(\Delta A_1/\Delta t_1)$) was set at 100%. The activities were determined under analogous conditions, in the presence of an inhibitor ($\Delta A_2/\Delta t_2$). The inhibitory action or lessening of enzyme activity then corresponds to: $100\% - (\Delta A_2/\Delta t_2)/(\Delta A_1/\Delta t_1)\%$.

Inhibitory effect on the trypsin or chymotrypsin activity**Example 1: Phenylboric acid as inhibitor in the enzyme test**

Phenylboric acid concentration (w/v*)	Inhibitory effect (lowering of trypsin activity)	Inhibitory effect (lowering of chymo-trypsin activity)
0 %	0 %	0 %
0.001 %	No inhibitory effect measurable	
0.005 %	No inhibitory effect measurable	Not tested
0.01 %	No inhibitory effect measurable	9 %
0.05%	5 %	45 %
0.1%	22 %	92 %

* weight per volume

The activity of trypsin in the concentration range selected is only moderately influenced by phenylboric acid. On the other hand, a clear concentration-dependent inhibition of chymotrypsin is observed.

Example 2: Boric acid as inhibitor in the enzyme test

Boric acid concentration (w/v*)	Inhibitory effect (lowering of trypsin activity)	Inhibitory effect (lowering of chymo-trypsin activity)
0 %	0 %	0 %
0.001 %	No inhibitory effect measurable	No inhibitory effect measurable
0.01 %	No inhibitory effect measurable	No inhibitory effect measurable
0.1 %	6 %	23%
0.5%	23 %	Not tested

* weight per volume

The inhibitory effect of boric acid on trypsin and chymotrypsin in the tested concentration range is only weak. Chymotrypsin is more strongly inhibited than trypsin for lower concentrations of boric acid.

Example 3: 4-(2-Aminoethyl)phenylsulfonyl fluoride (Pefabloc® SC) as inhibitor in enzyme test

Pefabloc® SC Concentration	Inhibitory effect (lowering of trypsin activity)	Inhibitory effect (lowering of chymo-trypsin activity)
0 %	0 %	0 %
0.0005 %	8 %	Not tested
0.001 %	Not tested	2 %
0.005 %	54 %	13 %
0.01%	74 %	29 %
0.02 %	95 %	Not tested
0.025 %	Not tested	54 %
0.04 %	100 %	Not tested
0.05 %	Not tested	73 %

* weight per volume

Pefabloc® SC in the concentration range tested shows a strong, concentration-dependent inhibition of trypsin and chymotrypsin.

Example 4: Pentapeptide sequence GPFPL as inhibitor in the enzyme test

N-CBZ-GPFPL concentration (w/v*)	Inhibitory effect (lowering of trypsin activity)	Inhibitory effect (lowering of chymo-trypsin activity)
0.03 %	No inhibitory effect measurable	2 %
0.06 %	- “ -	7 %
0.335 %	- “ -	27 %

* weight per volume

The trypsin activity is not affected by GPFPL in the concentration range chosen. At a concentration of the inhibitor of 0.33% by weight, a specific inhibition (27%) of chymotrypsin is demonstrated.

Example 5: Rosmarinic acid as inhibitor in the enzyme test

Rosmarinic acid concentration (w/v*)	Inhibitory effect (lowering of trypsin activity)	Inhibitory effect (lowering of chymo-trypsin activity)
0 %	0 %	0 %
0.001 %	Not tested	No inhibitory effect measurable
0.005 %	Not tested	2 %
0.0075 %	Not tested	7 %
0.01%	61 %	Not tested**
0.05%	95 %	Not tested**

* weight per volume

**: because of discoloration by rosmarinic acid, these concentrations could not be tested.

Rosmarinic acid displays a strong, concentration-dependent inhibition of trypsin. The inhibition of chymotrypsin is low for the low inhibitor concentrations that could be investigated

Example 6: Elhibin® as the inhibitor in the enzyme test

Elhibin® concentration (v/v*)	Inhibitory effect (lowering of trypsin activity)	Inhibitory effect (lowering of chymo-trypsin activity)
0 %	0 %	0 %
0.01 %	8 %	7 %
0.05 %	39 %	30 %
0.01 %	76 %	55 %
0.05%	98 %	92 %
1.0 %	Not tested	97 %

* v/v: volume per volume

Both trypsin and chymotrypsin are inhibited equally strongly by Elhibin® in the concentration range tested.

Example 7: t-AMCHA as the inhibitor in the enzyme test

t-AMCHA® SC concentration (w/v*)	Inhibitory effect (lowering of trypsin activity)	Inhibitory effect (lowering of chymo-trypsin activity)
0.01 %	9 %	No inhibitory effect measurable
0.05 %	36 %	- “ -
0.1 %	51 %	- “ -
0.5 %	85 %	- “ -
1.0 %	93 %	- “ -

* weight per volume

Only the trypsin activity is affected by t-AMCHA as a function of the inhibitor concentration. On the other hand, the activity of chymotrypsin in the same range of concentration is not affected by t-AMCHA.

Evaluation of the tests:

The test results show that the inhibitor t-AMCHA (Example 7) in the range of concentration investigated only inhibits trypsin and thus differs from the other inhibitors used in accordance with the invention. Some of the inhibitors tested achieve effective inhibition at a very low concentration.

Specific inhibition of the chymotrypsin activity was observed for low concentrations of the pentapeptide GPFPL. Boric acid shows a weak inhibition of both enzymes in the concentration range tested. At a low concentration (0.1%), phenylboric acid already shows a weak inhibition of trypsin and a strong inhibition of chymotrypsin. An almost complete inhibition of both enzymes also occurs with Elhibin® (0.5%). Low concentrations of rosmarinic acid (0.05%) are an extremely effective inhibitor for trypsin. Pefabloc® has also been shown to be an effective inhibitor of both enzymes, with trypsin being more strongly inhibited than chymotrypsin in the concentration range tested.

2. Tests of the inhibitors on skin biopsies

The influence of the protease inhibitors phenylboric acid, boric acid, the pentapeptide N-CBZ-Gly-Pro-Phe-Pro-Leu, rosmarinic acid and Elhibin® on the desquamation of the stratum corneum was investigated on skin biopsies.

Pieces of skin (8 mm²) were stamped out of fresh human skin explantations (from mammary reduction) and treated with a mixture of detergents (Na dodecylsulfate, N,N-dimethyldodecylamine oxide) in the absence and in the presence of inhibitors. Under the influence of the detergents, an intensified flaking-off (desquamation) of the horny layer (stratum corneum) is artificially induced, thus the formation of dry skin is simulated in the experiment. The number of corneal cells (corneocytes) flaked off was determined under the microscope in a Schilling counting chamber. A reduction in the corneocyte count indicates an inhibitory action of the potential inhibitors tested.

Method:

The inhibitors were added in the appropriate concentrations (cf. Tables for Examples 7-12) in the incubation buffer. This consisted of 0.1 M TRIS-HCl buffer (pH 8) with 0.1% by weight Na azide and the detergents Na dodecylsulfate (0.2 mM) and N,N-dimethyldodecylamine oxide (8 mM) as well as EDTA (5 mM). These incubation buffer solutions with varying concentrations of the inhibitor are then designated as test solutions.

Two types of blind controls were carried out, a positive and a negative control. For the so-called positive control only the incubation buffer was used, i.e. without the addition of inhibitors. For the so-called negative control a 5 mM solution of EDTA in TRIS-HCl buffer was added, i.e. without addition of the detergents.

For each reaction sample, 0.5 ml of the respective test solution or of the buffer mixture used for the blind controls was placed in sealable reaction vessels. All samples were carried out in quadruplicate in order to assure the reproducibility of the results.

After explantation, the human skin was transported in a dry, sterile Petri dish in a refrigerated container. After removal of the subcutaneous fat and connective tissue, 8mm²-sized pieces of skin were prepared using sterile stamps. These were washed for 15-20 min in sterile physiological NaCl (0.9%), added to the reaction samples (1 piece of skin/reaction sample) and incubated for 44 hours at 37°C.

After completion of the incubation phase, the reaction vessels were shaken for 30 seconds on a Vortex mixer to remove loosely adhering corneocytes from the pieces of skin. The pieces of skin were removed and the remaining dispersion was centrifuged for 8 minutes at 11,000 rpm to isolate the corneocytes. The detergent-containing supernatant liquid (0.4 ml) was discarded and the residue washed with 0.4 ml dist. water. After repeat centrifuging, the supernatant liquid (0.4 ml) was again discarded, the remaining cell pellet taken up in 0.4 ml dist. water and the loosened corneocytes were counted in a Schilling counting chamber under an optical microscope.

The following tables give a compilation of the number of loosened corneocytes:

- after treatment of the skin biopsies with a detergent mixture in the absence of the inhibitors (positive control)
- after treatment of the skin biopsies with a buffer solution in the absence of detergents and inhibitors (negative control)
- after treatment of the skin biopsies with a detergent mixture that contains the inhibitors in various concentrations.

Example 8: Phenylboric acid as inhibitor in the desquamation test

Phenylboric acid was tested in different concentrations as a desquamation inhibitor. The corneocyte value of the positive control was set at 100%.

Sample	Desquamation on human skin <i>ex vivo</i>
Positive control	100 %
Negative control	1.4 %
Phenylboric acid 0.05%	89.0%
Phenylboric acid 0.1%	60.0%

*: weight per volume

At a concentration of 0.1%, phenylboric acid could significantly reduce the flaking off of the corneocytes.

Example 9: Boric acid as inhibitor in the desquamation test

Boric acid was tested in different concentrations as a desquamation inhibitor. The corneocyte value of the positive control was set at 100%.

Sample	Desquamation on human skin <i>ex vivo</i>
Positive control	100 %
Negative control	0 %
Boric acid 0.01 %	86 %
Boric acid 0.1 %	50 %
Boric acid 0.2 %	47 %

*: weight per volume

At a concentration of 0.2%, boric acid could significantly reduce the flaking off of corneocytes.

Example 10: Pefabloc® SC as inhibitor in the desquamation test

Pefabloc® SC was tested in different concentrations as a desquamation inhibitor. The corneocyte value of the positive control was set at 100%.

Sample	Desquamation on human skin <i>ex vivo</i>
Positive control	100 %
Negative control	3 %
Pefabloc® 0.01 %	34 %
Pefabloc® 0.5 %	11 %

*: weight per volume

When 0.5% Pefabloc® SC was used the flaking off was reduced by about 90%.

Example 11: Z-GPFPL as inhibitor in the desquamation test

The pentapeptide N-CBZ-Gly-Pro-Phe-Pro-Leu (GPFPL) was tested at different concentrations as a desquamation inhibitor. The corneocyte value of the positive control was set at 100%.

Sample	Desquamation on human skin <i>ex vivo</i>
Positive control	100 %
Negative control	1 %
Z-GPFPL 0.1 %	93 %
Z-GPFPL 0.5 %	51 %

*: weight per volume

When 0.5% of the pentapeptide was used the flaking off was reduced by about one half.

Example 12: Rosmarinic acid as inhibitor in the desquamation test

Rosmarinic acid was tested in different concentrations as a desquamation inhibitor. The corneocyte value of the positive control was set at 100%.

Sample	Desquamation on human skin <i>ex vivo</i>
Positive control	100 %
Negative control	2.5 %
Rosmarinic acid 0.1 %	82.5 %
Rosmarinic acid 0.5 %	60.0 %
Rosmarinic acid 1.0 %	33.8 %

*: weight per volume

Rosmarinic acid also effectuated a concentration-dependent reduction in the flaking off of corneocytes. When 1.0% rosmarinic acid was used, the flaking off can be reduced by 33.8%.

Example 13. Elhibin® as inhibitor in the desquamation test

Elhibin® was tested in different concentrations as a desquamation inhibitor. The corneocyte value of the positive control was set at 100%.

Sample	Desquamation on human skin <i>ex vivo</i>
Positive control	100 %
Negative control	1.4 %
Elhibin® 0.2 %	13.9 %
Elhibin® 0.5 %	9.4 %
Elhibin® 1.0 %	8.9 %

*: volume per volume

Elhibin also acts in low concentration as a strong desquamation inhibitor and with respect to the flaking off of corneocytes in the concentration range investigated shows a weakly concentration-dependent profile.

Example 14: t-AMCHA as inhibitor in the desquamation test

t-AMCHA was tested in different concentrations as a desquamation inhibitor. The corneocyte value of the positive control was set at 100%.

Sample	Desquamation on human skin <i>ex vivo</i>
Positive control	100 %
Negative control	1.4 %
t-AMCHA 0.5 %	51.3 %
t-AMCHA 1.0 %	44.0 %
t-AMCHA 2.5 %	37.1 %

*: weight per volume

t-AMCHA is also shown to be a desquamation inhibitor with a concentration-dependent profile. However, the t-AMCHA concentration is comparatively higher to achieve a corresponding reduction in the desquamation.

Evaluation of the tests:

The desquamation of the human skin caused by the detergent mixture can be significantly reduced by means of phenylboric acid, boric acid, the pentapeptide Z-Gly-Pro-Phe-Pro-Leu, rosmarinic acid, Elhibin® and t-AMCHA. Concentration-dependent effects were shown, i.e. the flaking off of corneocytes decreases with an increase in the inhibitor concentration.

Examples of formulations in accordance with the invention

All the amounts given below are based on % by weight of the commercial substance or substance mixture based on the total amount of the composition (EO = added moles of ethylene oxide).

1. Shower gel

7.0% Sodium laureth sulfate (e.g. Texapon® N70)
 5.0% Sodium PEG-6-cocamidocarboxylate (e.g. Akypo-Soft® KA 250 BVC)
 4.0% Lauryl glucoside (e.g. Plantacare® 1200 UP)
 6.0% PEG-7-glyceryl cocoate (e.g. Cetiol® HE)
 0.2% Castor oil polyglycol ether, hardened (e.g. Eumulgin® HRE 455)
 8.0% Laureth-2 (e.g. Arlypon® F)
 1.0% Isopropyl myristate
 1.0% Perfume oil
 0.08% Polyquaternium-7 (e.g. Conditioner® P7)
 1.0% Sodium chloride
 0.25% Citric acid
 0.4% Sodium benzoate
 0.2% Salicylic acid
 4.0% Elhibin® or 1% Pefabloc® SC
 Water (dist) to 100%

Isopropyl myristate, perfume oil, Eumulgin® HRE 455 and Cetiol® HE were mixed. The other components were dissolved in order in water. Then the mixture of the oil components and the water-free surfactants were incorporated into the aqueous solution. Finally, the Arlypon F was added and the viscosity was adjusted with NaCl.

2. Foam bath

15.0% Sodium laureth sulfate (e.g. Texapon® N70)
7.0% Lauryl glucoside (e.g. Plantacare® 1200 UP)
3.0% N,N-Dimethyl-N-(cocoamidopropyl)ammonium acetobetaine (e.g. Dehyton® PK 45)
0.2% Castor oil polyglycol ether, hardened (e.g. Eumulgin® HRE 455)
1.0% PEG-7-glyceryl cocoate (e.g. Cetiol® HE)
1.0% Glycerol
0.5% Lactic acid
0.08% Polyquaternium-7 (e.g. Conditioner® P7)
0.4% Sodium benzoate
3.0% 4-(2-Aminoethyl)phenylsulfonyle fluoride (e.g. Pefabloc® SC)
0.9% Sodium chloride
1.0% Perfume oil
0.2% Citric acid
2.0% Pearllizing agent (e.g. Euperlan® PK 810)
q.s. colorant
Water (dist) to 100%

3. Anti-dandruff shampoo

15.0% Sodium laureth sulfate (e.g. Texapon® N70)
7.0% Disodium cocamphodiecetate (e.g. Rewoteric® AM 2C/NM)
2.0% Pearllizing agent (e.g. Euperlan® PK 810)
0.08% Polyquaternium-10 (e.g. Polymer JR® 400)
2.0% Elhibin®
0.2% Preservative
q.s. Citric acid
q.s. Sodium chloride
Water (dist) to 100%

4. Hand dishwashing rinsing agent concentrate (Skeleton formulation)

25.0% Sodium laureth sulfate (e.g. Texapon® NSO)
3.0% C₁₂₋₁₆-Alkylpolyglucoside (e.g. Plantacare® 1200 UP)
2.0% Cocamidopropylbetaine (e.g. Tego-Betaine® BL-215)
8.0% Ethanol (96%)
3.0% Polycarboxylate, Na salt
0.5% Citric acid
0.4% Preservative
0.3% Perfume
3.0% Rosmarinic acid
Water (dist) to 100%

5. Cleaner (skeleton formulation)

2.0% Sodium laureth sulfate (e.g. Texapon® NSO)
10.0% C₁₂₋₁₆-Alkylpolyglucoside (e.g. Plantacare® 1200 UP)
1.0% Cocamidopropylbetaine (e.g. Tego-Betaine® BL-215)
5.0% Ethanol (96%)
1.5% Sodium chloride
3.0% Citric acid
3.0% Urea
0.4% Preservative
2.0% Perfume
4.0% Rosmarinic acid
Water (dist) to 100%

Appendix**List of trade names of raw materials used**

1) Tego-Betain® BL-215

INCI: Cocamidopropyl betaine

Hersteller: Goldschmidt

Hersteller = Manufacturer;

2) Texapon® NSO

INCI: Sodium laureth sulfate

Hersteller: Cognis Deutschland GmbH (Henkel)

Hersteller = Manufacturer;

3) Dehyton® PK 45

INCI: Aqua (water), Cocamido propyl betaine

Hersteller: Goodrich

4) Euperlan® PK 810

INCI: Aqua (Wasser), Glycol distearate, Sodium laureth sulfate,

Cocamide MEA, Laureth-10, Formic acid

Hersteller: Cognis Deutschland GmbH (Henkel)

Wasser = water

5) Rewotenic® AM2C/NM

INCI: Disodium cocamphodiacetate

Hersteller: CK Witco (Rewo)

6) Polymer JR® 400

INCI: Polyquaternium-10

Hersteller: National Starch

7) Eurnalgin® HRE 455

INCI: PEG-40-hydrogenated castor oil, propylene glycol, aqua (water)

Hersteller: Cognis Deutschland GmbH (Henkel)

8) Cetiol® HE

INCI: PEG-7-Glycerol cocoate

Hersteller: Cognis Deutschland GmbH (Henkel)

9) Pefabloc®

4-(2-Aminoethyl)phenylsulfonylfluorid

Hersteller: Boehringer Mannheim

10) Pefabloc® SC

4-(2-Aminoethyl)phenylsulfonylfluorid mit speziellem Protector

Hersteller: Boehringer Mannheim

mit speziellem Protector = with special protector

11) Texapon® N 70

Natriumlaurethsulfat

Hersteller: Cognis Deutschland GmbH (Henkel)

12) Akypo-Soft® KA 250 BYC

INCI: Sodium-PEG-6-cocamide carboxylate

Hersteller: Kao Chemicals

13) Plantacare® 1200 UP

INCI: Lauryl glucoside

Hersteller: Cognis Deutschland GmbH (Henkel)

14) Arlypon® F

INCI: Laureth-2

Hersteller: Cognis Deutschland GmbH (Henkel)

15) Conditioner® P7

INCI: Polyquaternium-7

Hersteller: Sigma, Bergamo (Sivax)

Patent Claims

1. Cleaning agent containing surfactant, characterized by the fact that it contains at least one inhibitor for the proteinases involved in the degradation of the desmosomes, which in a concentration of at least 0.0005% by weight has an inhibition of at least 5%.
2. Agent as in claim 1, characterized by the fact that the inhibitors are chosen from the group: boric acid and/or its derivatives, 4-(2-aminoethyl)phenylsulfonyl fluoride, compounds containing the peptide sequence glycine-proline-phenylalanine-proline-leucine, rosmarinic acid and Elhibin®.
3. Agent as in one of the claims 1 to 2, characterized by the fact that it contains at least one inhibitor that inhibits the serine-proteinases involved in the degradation of the desmosomes.
4. Agent as in one of the claims 1 to 3, characterized by the fact that it contains at least one inhibitor that inhibits the proteinases of the type of trypsin- or chymotrypsin-like serine proteinases involved in the degradation of the desmosomes.
5. Agent as in one of the claims 1 to 4, characterized by the fact that it contains boric and/or its derivatives as an inhibitor.
6. Agent as in one of the claims 1 to 4 characterized by the fact that it contains 4-(2-aminoethyl)phenylsulfonyl fluoride as an inhibitor.
7. Agent as in one of the claims 1 to 4, characterized by the fact that it contains as an inhibitor a chemical compound containing the pentapeptide sequence glycine-proline-phenylalanine-proline-leucine (GPFPL).
8. Agent as in one of the claims 1 to 4 characterized by the fact that it contains rosmarinic acid as an inhibitor.
9. Agent as in one of the claims 1 to 4 characterized by the fact that it contains the active agent Elhibin® obtained from leguminous seeds as an inhibitor.
10. Agent as in one of the claims 1 to 9 characterized by the fact that the inhibitors are contained in the composition in a concentration of ca. 0.0001 to 20% by weight.
11. Use of an agent as in one of the claims 1 to 10 for topical prophylactic and/or cosmetic treatment of dry skin.
12. Method for the cleansing of the skin and tegumentary appendages with simultaneous inhibition or diminishing of the drying out of the skin, characterized by the fact that the skin and tegumentary appendages are treated with a surfactant-containing agent as in one of the claims 1 to 10.
13. Method for the manual cleaning of hard surfaces with surfactant-containing cleaning agents with simultaneous inhibition or diminishing of the drying out of the skin, characterized by the fact that the surfaces are treated with a surfactant-containing cleaning agent in accordance with one of the claims 1 to 10.

INTERNATIONAL SEARCH REPORT

International Search Report Filed in Application No. PCT/EP 00/09832		
A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C11D3/02 C11D3/382 C11D3/34 C11D3/33 C11D3/16 A61K7/48		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Mailed documents searched (classification system followed by classification symbols) IPC 7 C11D A61K		
Unpublished documents searched (classification system followed by classification symbols) IPC 7 C11D A61K		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document with indication, where appropriate, of the relevant passages	Relevant to claim no.
X	DE 37 41 617 A (COLGATE PALMOLIVE CO) 7 July 1988 (1988-07-07) claims; examples	1-5, 10, 13
X	US 5 322 839 A (MUELLER CHRISTIAN ET AL) 21 June 1994 (1994-06-21) claims; examples	1-4, 9, 10, 12
X	GB 1 513 865 A (PROCTER & GAMBLE) 14 June 1978 (1978-06-14) claims; examples	1-4, 9, 10, 12, 13
X	WO 94 29428 A (PROCTER & GAMBLE) 22 December 1994 (1994-12-22) page 7 -page 9; claims; examples	1-5, 10
D. OTHER INFORMATION		
[X] Primary documents are listed in the classification of box C.		
[X] Patent family members are listed in Annex.		
* Special categories of cited documents		
"A" Document defining the general state of the art which is not considered to be of particular relevance		
"C" Earlier document but published on or after the international filing date		
"D" Document which may have double or priority claims; or which is cited to establish the publication date of another claim or other special reason (as specified)		
"E" Document referring to an oral disclosure, use, exhibition or other means		
"F" Document published prior to the international filing date but later than the priority date claimed		
"I" Later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention		
"K" Document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to further an inventive step when the document is taken alone		
"L" Document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is considered with one or more other such documents, such combination being obvious to a person skilled in the art		
"S" Document member of the same patent family		
Date of the actual completion of the international search:		Date of mailing of the international search report
29 January 2001		02/02/2001
Name and mailing address of the ISA European Patent Office, P.O. Box 18, Postbox 1 7430 - 2000 Metz, France Tel: (+31-70) 340-2040, Fax: (+31-70) 340-2041 Telex: (+31-70) 340-2041		Authorized officer Pfannenstern, H

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C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 96 01101 A (PROCTER & GAMBLE) 18 January 1996 (1996-01-18) page 2 - page 3; claims; examples II, IV	1-4, 10-12
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